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10/541,702	01/17/2006	Junichi Kawakami	236211	9790

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EXAMINER	
SZNAIDMAN, MARCOS L	

ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/541,702	KAWAKAMI, JUNICHI	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-12,20-22 and 27-40* is/are pending in the application.

4a) Of the above claim(s) *7-10,20,27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,12,21,22 and 29-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on April 4, 2008.

Receipt of Declarations under 37 CFR 1.131 and 1.132 is acknowledged.

Status of Claims

Amendment of claims 7 and 11, cancellation of claims 23-26 and addition of claims 29-40 is acknowledged.

Claims 7-12, 20-22, and 27-40 are currently pending and are the subject of this office action.

Claims 7-10, 20, and 27-28 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 21, 2007.

Claims 11-12, 21-22 and 29-40 are currently under examination.

Priority

The present application is a 371 of PCT/JP04/00105 filed 01/09/2004, and claims priority to foreign application: Japan 2003-004813 filed 01/10/2003.

Response to Arguments

This is in response to applicant's arguments, filed on April 4, 2008.

Claims rejected under 35 USC 112, first paragraph (written description).

Due to applicant's amendment of claims 7 and 11, the written description rejection is now moot.

Rejection under 35 USC 112, first paragraph (written description) is withdrawn.

Claims rejected under 35 USC 112, first paragraph (enablement).

Due to applicant's cancellation of claims 23-26, the enablement rejection is now moot.

Rejection under 35 USC 112, first paragraph (enablement) is withdrawn.

Claims rejected under 35 USC 103 (a)

Applicant's arguments have been fully considered but are not persuasive.

Applicant argues that the skilled in the art would have not been motivated to combine the teachings of Bourrie et. al. (PNAS, 1999, 96:12855-12859, cited in previous office action) and Watanabe et. al. (The Journal of Pharmacology and Experimental Therapeutics, 1994, 268:1597-1604, cited in previous application) because Watanabe et. al. does not disclose or suggest the use of edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one or MCI-186, species elected) to treat multiple sclerosis.

If Watanabe et. al. would have disclosed that edaravone can be used to treat multiple sclerosis, the Watanabe reference would have anticipated the claims. What Watanabe teaches is that: "3-methyl-1-phenyl-2-pyrazolin-5-one (MCI-186, edaravone)

mitigated dysfunction of the blood-brain barrier" (see abstract lines 6-7), and what Bourrie et. al. teaches is that: compounds that provide protection against blood-brain barrier dysfunction are good candidates for the treatment of multiple sclerosis (see abstract). So the skilled in the art would have been motivated to combine these two references and use edaravone (that according to Watanabe et. al. mitigates the blood-brain barrier dysfunction) for the treatment of multiple sclerosis (that according to Bourrie et. al. it can be treated with compounds that provide protection against blood-brain barrier dysfunction).

The evidence submitted in the 132 declaration is insufficient to overcome the rejection. First, there is non experiment using compound SR 57746A as a standard to show that the results of the reference have been duplicated correctly. Second, applicant demonstrates that edaravone does not inhibit lymphocytic infiltration in the lumbar part of the spinal cord; however applicant did not run the relevant experiment which is to compare the IgG index with and without treatment of drug, which is an indication of the ability of the drug to impair disruption the blood-brain barrier (see page 12856 under the title: SR 57746A impaired BBB disruption and CNS production of IgG during EAE).

Rejection under 35 USC 103 (a) is maintained.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or

newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 11-12 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Bourrie et. al. (PNAS, 1999, 96:12855-12859) in view of Watanabe et. al. (The Journal of Pharmacology and Experimental Therapeutics, 1994, 268:1597-1604, cited by applicant).

Claims 11-12 and 21-22 recite: "a method for treating multiple sclerosis, which comprises administering to a mammal having multiple sclerosis, an effective amount of

a pyrazolone derivative represented by the formula I (species elected: 3-methyl-1-phenyl-2-pyrazolin-5-one or edaravone or MCI-186).

For instant claims 11-12 and 21-22 Bourrie et. al teach that: "Experimental autoimmune encephalomyelitis (EAE) is a T cell autoimmune disorder that is a widely used animal model for multiple sclerosis (MS) and, as in MS, clinical signs of EAE are associated with blood-brain barrier (BBB) disruption. SR-57746A, a nonpeptide drug without classical immunosuppressive properties efficiently protected the BBB and impaired intrathecal IgG synthesis (two conventional markers of MS exacerbation) and consequently suppressed EAE clinical signs. This compound inhibited EAE-induced spinal cord mononuclear cell invasion and normalized tumor necrosis factor a and IFN-g mRNA expression within the spinal cord. These data suggested that pharmacological intervention aimed at inhibiting proinflammatory cytokine expression within the central nervous system provided protection against BBB disruption, the first clinical sign of EAE and probably the key point of acute MS attacks. This finding could lead to the development of a new class of compounds for oral therapy of MS, as a supplement to immunosuppressive agents." (see abstract). In other words, Bourrie et. al. clearly teaches that compounds that provide protection against blood-brain barrier dysfunction are good candidates for the treatment of multiple sclerosis.

Bourrie et. al. do not teach the treatment of multiple sclerosis by administering 3-methyl-1-phenyl-2-pyrazolin-5-one. However, Watanabe et. al. teach that: "3-methyl-1-phenyl-2-pyrazolin-5-one (MCI-186, edaravone) mitigated dysfunction of the blood-brain barrier" (see abstract lines 6-7).

At the time of the invention, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of Bourrie et. al, (that indicates that compounds that provide protection against blood-brain barrier dysfunction are good candidates for the treatment of multiple sclerosis), with the teachings of Watanabe et. al, (that indicates that 3-methyl-1-phenyl-2-pyrazolin-5-one reduces dysfunction of the blood-brain barrier), with the motivation of developing a treatment for multiple sclerosis by administering to a patient 3-methyl-1-phenyl-2-pyrazolin-5-one; thus resulting in the practice of claims 11-12 and 21-22 with a reasonable expectation of success.

Claims 29-40 are rejected under 35 U.S.C. 103 (a) as being unpatentable over applicant's own admission of prior arts in view of Watanabe et. al. (The Journal of Pharmacology and Experimental Therapeutics, 1994, 268:1597-1604, cited by applicant).

Claims 29-32 recite: "a method for treating meningitis, which comprises administering to a mammal having multiple sclerosis, an effective amount of a pyrazolone derivative represented by the formula I (species elected: 3-methyl-1-phenyl-2-pyrazolin-5-one or edaravone or MCI-186).

For instant claims 29-32 applicant admits (see page 1, last paragraph) that the prior art teaches that: "in the case of inflammatory diseases of central nervous system such as: multiple sclerosis, meningitis, cerebritis or brain abscess, it has been reported that the blood-brain barrier is disrupted."

Applicant's admission of the prior art does not teach the treatment of meningitis by administering 3-methyl-1-phenyl-2-pyrazolin-5-one. However, Watanabe et. al. teach that: "3-methyl-1-phenyl-2-pyrazolin-5-one (MCI-186, edaravone) mitigated dysfunction of the blood-brain barrier" (see abstract lines 6-7).

At the time of the invention, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of applicant's admission of prior art (that indicates that in meningitis the blood-brain barrier is disrupted), with the teachings of Watanabe et. al, (that indicates that 3-methyl-1-phenyl-2-pyrazolin-5-one reduces dysfunction of the blood-brain barrier), with the motivation of developing a treatment for meningitis by administering to a patient 3-methyl-1-phenyl-2-pyrazolin-5-one; thus resulting in the practice of claims 29-32 with a reasonable expectation of success.

Claims 33-36 recite: "a method for treating cerebritis, which comprises administering to a mammal having multiple sclerosis, an effective amount of a pyrazolone derivative represented by the formula I (species elected: (3-methyl-1-phenyl-2-pyrazolin-5-one or edaravone or MCI-186).

For instant claims 33-36 applicant admits (see page 1, last paragraph) that the prior art teaches that: "in the case of inflammatory diseases of central nervous system such as: multiple sclerosis, meningitis, cerebritis or brain abscess, it has been reported that the blood-brain barrier is disrupted."

Applicant's admission of the prior art does not teach the treatment of cerebritis by administering 3-methyl-1-phenyl-2-pyrazolin-5-one. However, Watanabe et. al. teach

that: "3-methyl-1-phenyl-2-pyrazolin-5-one (MCI-186, edaravone) mitigated dysfunction of the blood-brain barrier" (see abstract lines 6-7).

At the time of the invention, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of applicant's admission of prior art (that indicates that in cerebritis the blood-brain barrier is disrupted), with the teachings of Watanabe et. al, (that indicates that 3-methyl-1-phenyl-2-pyrazolin-5-one reduces dysfunction of the blood-brain barrier), with the motivation of developing a treatment for cerebritis by administering to a patient 3-methyl-1-phenyl-2-pyrazolin-5-one; thus resulting in the practice of claims 33-36 with a reasonable expectation of success.

Claims 37-40 recite: "a method for treating brain abscess, which comprises administering to a mammal having multiple sclerosis, an effective amount of a pyrazolone derivative represented by the formula I (species elected: (3-methyl-1-phenyl-2-pyrazolin-5-one or edaravone or MCI-186).

For instant claims 37-40 applicant admits (see page 1, last paragraph) that the prior art teaches that: "in the case of inflammatory diseases of central nervous system such as: multiple sclerosis, meningitis, cerebritis or brain abscess, it has been reported that the blood-brain barrier is disrupted."

Applicant's admission of the prior art does not teach the treatment of brain abscess by administering 3-methyl-1-phenyl-2-pyrazolin-5-one. However, Watanabe et. al. teach that: "3-methyl-1-phenyl-2-pyrazolin-5-one (MCI-186, edaravone) mitigated dysfunction of the blood-brain barrier" (see abstract lines 6-7).

At the time of the invention, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of applicant's admission of prior art (that indicates that in brain abscess the blood-brain barrier is disrupted), with the teachings of Watanabe et. al, (that indicates that 3-methyl-1-phenyl-2-pyrazolin-5-one reduces dysfunction of the blood-brain barrier), with the motivation of developing a treatment for brain abscess by administering to a patient 3-methyl-1-phenyl-2-pyrazolin-5-one; thus resulting in the practice of claims 37-40 with a reasonable expectation of success.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward can be reached on 571 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1611
July 15, 2008

/MP WOODWARD/
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